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TO: Devesh Khare **Location: cm1/8a13/8b19** **Art Unit : 1623** **Tuesday, November 18, 2003** **Case Serial Number: 10/007489**	**From : Susan Hanley** **Location: Biotech-Chem Library** **CM1 6B05** **Phone: 305-4053** **susan.hanley@uspto.gov**

Search Notes

mg

Commercial Database Search Request

10/15/03

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○ TC 2800 ○ TC 3600 ○ TC 3700 ○ Other

Enter your Contact Information below:

Name: Devesh Khare

Employee Number: 77931 Phone: 605-1199

Art Unit or Office: 1623 Building & Room Number: 8 A 13, Mail 8 B19

Enter the case serial number (Required): 10/007,489

If not related to a patent application, please enter NA here.

Class / Subclass(es) 536/25.34

Earliest Priority Filing Date: 09/14/1998

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Provide detailed information on your search topic:

- In your own words, describe in detail the concepts or subjects you want us to search.
- Include synonyms, keywords, and acronyms. Define terms that have special meanings.
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  Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers

- *For Sequence Searches Only*
  Include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.
- *For Foreign Patent Family Searches Only*
  Include the country name and patent number.
- Provide examples or give us relevant citations, authors, etc., if known.
- FAX or send the **abstract, pertinent claims** (not all of the claims), **drawings, or chemical structures** to your EIC or branch library.

Enter your Search Topic Information below:

Please search the following claims:

Claim 1: A method for generating phosphorothioate oligo mixtures comprising:
1) growing a single-stranded recombinant DNA phage in modified media that uses thio-phosphate as a source of phosphate

2)harvesting the single-stranded phage and purifying the DNA corresponding to the recombinant DNA insert

3) fragmentation of the insert DNAsuch that oligo mixtures spanning the entire length of the segment are generated

Claim 2: the method of claim 1 used to generate phosphorothioate ds DNA, ss DNA, and/or RNA by in vivo incorporation of thio-phosphate into nucleotide precursor pools.

Thank you.
devesh khare

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Press ALT + F, then P to print this screen for your own information.

SEND RESET

007, 489

```
=> file medline
FILE 'MEDLINE' ENTERED AT 14:47:28 ON 18 NOV 2003

 FILE LAST UPDATED: 13 NOV 2003 (20031113/UP).  FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l58

L55         546 SEA FILE=MEDLINE ABB=ON  PLU=ON  10101-88-9 OR THIOPHOSPHORIC
                OR 13598-51-1
L56           3 SEA FILE=MEDLINE ABB=ON  PLU=ON  L55 AND (SSDNA OR SINGLE-STRAN
                D? OR SS DNA)
L57        2090 SEA FILE=MEDLINE ABB=ON  PLU=ON  ORGANOTHIOPHOSPHORUS COMPOUNDS
                /CT
L58           1 SEA FILE=MEDLINE ABB=ON  PLU=ON  L56 AND L57


=> file embase

FILE 'EMBASE' ENTERED AT 14:47:29 ON 18 NOV 2003
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 FILE COVERS 1974 TO 13 Nov 2003 (20031113/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
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=> d que l73

L64         962 SEA FILE=EMBASE ABB=ON  PLU=ON  10101-88-9 OR THIOPHOSPHORIC
                OR 13598-51-1 OR THIOPHOSPHATE
L65          69 SEA FILE=EMBASE ABB=ON  PLU=ON  L64 AND (SSDNA OR SINGLE-STRAND
                ? OR SS DNA OR ?PHAGE OR PLASMID)
L66          38 SEA FILE=EMBASE ABB=ON  PLU=ON  L65 AND ?OLIGO?
L70          15 SEA FILE=EMBASE ABB=ON  PLU=ON  L66 AND (HIGH OR THIOPHOSPHATE
                OR PHOSPHOROTHIOATE OR EXTENDING)/TI
L71           3 SEA FILE=EMBASE ABB=ON  PLU=ON  L70 NOT (CHIRAL OR EFFECT OR
                VIRAL OR VIVO  OR ANTIPARALLEL OR SFII OR MICE OR MACROPHAGE
                OR GENE OR CPG)/TI
L72           1 SEA FILE=EMBASE ABB=ON  PLU=ON  L66 AND EXTENDING/TI
L73           4 SEA FILE=EMBASE ABB=ON  PLU=ON  L71 OR L72


=> file hcaplus

FILE 'HCAPLUS' ENTERED AT 14:47:30 ON 18 NOV 2003
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FILE COVERS 1907 - 18 Nov 2003  VOL 139 ISS 21
FILE LAST UPDATED: 17 Nov 2003  (20031117/ED)

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```
=> d que l10

L1  (      1813)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PHOSPHOROTHIOATE OLIGONUCLEOTI
               DES+PFT,NT/CT
L2          231 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1(L)PREP/RL
L4            5 SEA FILE=REGISTRY ABB=ON  PLU=ON  O3PS/MF
L5         8754 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PHOSPHOROTHIOATE"
L6          448 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 AND M/ELS
L7           35 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT C/ELS
L8           40 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 OR L7
L9          354 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8
L10           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 AND L2


=> d que l19

L3          1813 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PHOSPHOROTHIOATE OLIGONUCLEOTI
               DES+PFT,NT/CT
L4             5 SEA FILE=REGISTRY ABB=ON  PLU=ON  O3PS/MF
L5          8754 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PHOSPHOROTHIOATE"
L6           448 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 AND M/ELS
L7            35 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT C/ELS
L8            40 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 OR L7
L9           354 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8
L16       222353 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DNA+PFT/CT
L17         5268 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)(SS OR SINGLE-STRAND?)
L18           24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND L3
L19            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 AND L18


=> d que l23

L3          1813 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PHOSPHOROTHIOATE OLIGONUCLEOTI
               DES+PFT,NT/CT
L16       222353 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DNA+PFT/CT
L17         5268 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)(SS OR SINGLE-STRAND?)
L18           24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND L3
L20       486562 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (MONOTHIO? OR PHOSPHOROTHIO?
               OR THIO? OR PHOSPHOROMONOTHIO?)
L21           24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L20 AND L18
L22            3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 AND (PHAGE OR BACTERIOPHAG
               E)
L23            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 NOT CIRCULAR/TI


=> d que l25

L1  (      1813)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PHOSPHOROTHIOATE OLIGONUCLEOTI
               DES+PFT,NT/CT
L2          231 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1(L)PREP/RL
L16       222353 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DNA+PFT/CT
L17         5268 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16(L)(SS OR SINGLE-STRAND?)
L24           12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 AND (PHAGE OR BACTERIOPHAGE
               )
L25            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 AND L17


=> d que l41

L4             5 SEA FILE=REGISTRY ABB=ON  PLU=ON  O3PS/MF
L5          8754 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PHOSPHOROTHIOATE"
L6           448 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5 AND M/ELS
L7            35 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT C/ELS
L8            40 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 OR L7
L9           354 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8
L32          354 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 AND L5
L33           11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L32 AND SINGLE-STRAND?
L39           10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND ?OLIGO?
L40           10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L39 AND ?THIO?
L41            7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L40 NOT (GOLD OR DOUBLE OR
               HAPLOTYPES)/TI


=> s l10 or l19 or l23 or l25 or l41

L74           12 L10 OR L19 OR L23 OR L25 OR L41

=> dup rem l58 l73 l74
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FILE 'MEDLINE' ENTERED AT 14:47:58 ON 18 NOV 2003

FILE 'EMBASE' ENTERED AT 14:47:58 ON 18 NOV 2003

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PROCESSING COMPLETED FOR L73
PROCESSING COMPLETED FOR L74
L75 17 DUP REM L58 L73 L74 (0 DUPLICATES REMOVED)
ANSWER '1' FROM FILE MEDLINE
ANSWERS '2-5' FROM FILE EMBASE
ANSWERS '6-17' FROM FILE HCAPLUS

=> d ibib abs ind 1-5

L75 ANSWER 1 OF 17 MEDLINE on STN
ACCESSION NUMBER: 85054878 MEDLINE
DOCUMENT NUMBER: 85054878 PubMed ID: 6094546
TITLE: Cleavage of phosphorothioate-substituted DNA by restriction endonucleases.
AUTHOR: Potter B V; Eckstein F
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1984 Nov 25) 259 (22) 14243-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198412
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19841227

AB M13 RF DNA was synthesized in vitro in the presence of various single deoxynucleoside 5'-O-(1-thiotriphosphate) phosphorothioate analogues, and the three other appropriate deoxynucleoside triphosphates using a M13 (+)-single-stranded template, Escherichia coli DNA polymerase I and T4 DNA ligase. The resulting DNAs contained various restriction endonuclease recognition sequences which had been modified at their cleavage points in the (-)-strand by phosphorothioate substitution. The behavior of the restriction enzymes AvaI, BamHI, EcoRI, HindIII, and SalI towards these substituted DNAs was investigated. EcoRI, BamHI, and HindIII were found to cleave appropriate phosphorothioate-substituted DNA at a reduced rate compared to normal M13 RF DNA, and by a two-step process in which all of the DNA is converted to an isolable intermediate nicked molecule containing a specific discontinuity at the respective recognition site presumably in the (+)-strand. By contrast, SalI cleaved substituted DNA effectively without the intermediacy of a nicked form. AvaI, however, is only capable of cleaving the unsubstituted (+)-strand in appropriately modified DNA.

CT Check Tags: Support, Non-U.S. Gov't
Bacteriophage phi X 174: GE, genetics
Base Sequence
Binding Sites
*DNA Restriction Enzymes: ME, metabolism
*DNA, Single-Stranded: AN, analysis
DNA, Viral: AN, analysis
Deoxyribonuclease BamHI
Deoxyribonuclease EcoRI
Deoxyribonuclease HindIII
*Organothiophosphorus Compounds: ME, metabolism
*Thiophosphoric Acid Esters: ME, metabolism

CN 0 (DNA, Single-Stranded); 0 (DNA, Viral); 0 (Organothiophosphorus Compounds); 0 (Thiophosphoric Acid Esters); EC 3.1.21 (DNA Restriction Enzymes); EC 3.1.21.- (Deoxyribonuclease BamHI); EC 3.1.21.- (Deoxyribonuclease EcoRI); EC 3.1.21.- (Deoxyribonuclease HindIII); EC 3.1.21.- (endodeoxyribonuclease AvaI); EC 3.1.21.- (endodeoxyribonuclease SalI)

L75 ANSWER 2 OF 17 EMBASE
on STN
ACCESSION NUMBER: 96053473 EMBASE
DOCUMENT NUMBER: 1996053473
TITLE: Extending the chemistry that supports genetic information transfer in vivo: Phosphorothioate DNA,

phosphorothioate RNA, 2'-O-methyl RNA, and methylphosphonate DNA.
AUTHOR: Thaler D.S.; Liu S.; Tombline G.
CORPORATE SOURCE: DNA RMCP, Jefferson Cancer Center, Thomas Jefferson University, 233 South 10th Street,Philadelphia, PA 19107, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1996) 93/3 (1352-1356). ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB DNA and RNA are the polynucleotides known to carry genetic information in life. Chemical variants of DNA and RNA backbones have been used in structure- function and biosynthesis studies in vitro, and in antisense pharmacology, where their properties of nuclease resistance and enhanced cellular uptake are important. This study addressed the question of whether the base(s) attached to artificial backbones encodes genetic information that can be transferred in vivo. **Oligonucleotides** containing chemical variants of DNA or RNA were used as primers for site-specific mutagenesis of **bacteriophage** f1. Progeny **phage** were scored both genetically and physically for the inheritance of information originally encoded by bases attached to the nonstandard backbones. Four artificial backbone chemistries were tested: phosphorothioate DNA, phosphorothioate RNA, 2'-O-methyl RNA and methylphosphonate DNA. All four were found capable of faithful information transfer from their attached bases when one or three artificial positions were flanked by normal DNA. Among **oligonucleotides** composed entirely of nonstandard backbones, only phosphorothioate DNA supported genetic information transfer in vivo.
CT Medical Descriptors:
*gene transfer
*nucleotide sequence
article
chemical structure
dna replication
dna synthesis
genetic code
molecular genetics
priority journal
site directed mutagenesis
structure activity relation
Drug Descriptors:
*dna
*rna
antisense oligonucleotide
oligonucleotide
phosphorothioic acid
transfer rna
RN (dna) 9007-49-2; (rna) 63231-63-0; (phosphorothioic acid) 10101-88-9, 13598-51-1, 15181-41-6; (transfer rna) 9014-25-9

L75 ANSWER 3 OF 17 EMBASE
on STN
ACCESSION NUMBER: 93173385 EMBASE
DOCUMENT NUMBER: 1993173385
TITLE: Site-directed mutagenesis of single-**stranded** and double-stranded DNA by **phosphorothioate** approach.
AUTHOR: Olsen D.B.; Sayers J.R.; Eckstein F.
SOURCE: Methods in Enzymology, (1993) 217/- (189-217). ISSN: 0076-6879 CODEN: MENZAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
CT Medical Descriptors:
*site directed mutagenesis
article
bacteriophage t7
cell transformation
dna sequence
dna synthesis
dna template

escherichia coli
gene mutation
hydrolysis
nonhuman
nucleotide sequence
plasmid
polymerization
priority journal
Drug Descriptors:
*double stranded dna
*phosphorothioic acid
***plasmid dna**
***single stranded dna**
dna polymerase
ethidium bromide
exodeoxyribonuclease iii
oligonucleotide
primer dna
restriction endonuclease
RN (phosphorothioic acid) 10101-88-9, 13598-51-1, 15181-41-6; (dna polymerase) 37217-33-7; (ethidium bromide) 1239-45-8; (exodeoxyribonuclease iii) 9037-44-9

L75 ANSWER 4 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 90080670 EMBASE
DOCUMENT NUMBER: 1990080670
TITLE: High-efficiency **oligonucleotide** -directed **plasmid** mutagenesis.
AUTHOR: Olsen D.B.; Eckstein F.
CORPORATE SOURCE: Max-Plank Institut fur, Experimentelle Medizin, Abteilung Chemie, Hermann-Rein Strasse 3,D-3400 Gottingen, Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1990) 87/4 (1451-1455). ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A number of single- and double-base substitutions have been introduced into either the polylinker region or the lacZ gene in the **plasmid** vector pUC19. The efficiencies of these changes upon transfection of TG-1 bacterial cells were generally 70-80%. A strategy has been devised by which the wild-type DNA can be selectively destroyed. It is primarily based on the resistance of phosphorothioate internucleotide linkages to some restriction enzymes. A mismatch **oligonucleotide** is introduced into a gapped region and the gap is filled using three deoxynucleoside 5'-triphosphates and one deoxynucleoside 5'-[.alpha.-thio]triphosphate. Reaction with a restriction enzyme that is unable to hydrolyze phosphorothioates ensures that the DNA containing the mismatch **oligonucleotide** is only nicked. Concomitantly, the DNA that does not contain the desired mutation is linearized. Subsequent reactions with an exonuclease and DNA polymerase I yield mutant homoduplex DNA for transfection.
CT Medical Descriptors:
***plasmid**
*site directed mutagenesis
genetic engineering
nonhuman
article
priority journal
Drug Descriptors:
*phosphorothioic acid
RN (phosphorothioic acid) 10101-88-9, 13598-51-1, 15181-41-6

L75 ANSWER 5 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 90371788 EMBASE
DOCUMENT NUMBER: 1990371788
TITLE: Chemical and enzymatic ligation of 5'-**thiophosphates of oligodeoxyribonucleotides**
AUTHOR: Oshevskii S.I.
CORPORATE SOURCE: Institute of Cytology and Genetics, Siberian Branch of the Academy of Sciences of the USSR, Novosibirsk, Russia

SOURCE: Doklady Biochemistry, (1990) 310/1-6 (15-18).
ISSN: 0012-4958 CODEN: DBIOAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
CT Medical Descriptors:
bacteriophage t4
article
Drug Descriptors:
*dna
***oligonucleotide**
*rna
RN (dna) 9007-49-2; (rna) 63231-63-0

=> d ibib abs hitrn 6

L75 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:461948 HCAPLUS
DOCUMENT NUMBER: 139:225986
TITLE: Comparison of different antisense strategies in mammalian cells using locked nucleic acids, 2'-O-methyl RNA, **phosphorothioates** and small interfering RNA
AUTHOR(S): Gruenweller, Arnold; Wyszko, Eliza; Bieber, Birgit; Jahnel, Ricarda; Erdmann, Volker A.; Kurreck, Jens
CORPORATE SOURCE: Institut fuer Chemie-Biochemie, Freie Universitaet Berlin, Berlin, D-14195, Germany
SOURCE: Nucleic Acids Research (2003), 31(12), 3185-3193
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Locked nucleic acids (LNAs) and double-stranded small interfering RNAs (siRNAs) are rather new promising antisense mols. for cell culture and in vivo applications. Here, we compare LNA-DNA-LNA gapmer **oligonucleotides** and siRNAs with a **phosphorothioate** and a chimeric 2'-O-Me RNA-DNA gapmer with respect to their capacities to knock down the expression of the vanilloid receptor subtype 1 (VR1). LNA-DNA-LNA gapmers with four or five LNAs on either side and a central stretch of 10 or 8 DNA monomers in the center were found to be active gapmers that inhibit gene expression. A comparative co-transfection study showed that siRNA is the most potent inhibitor of VR1-green fluorescent protein (GFP) expression. A specific inhibition was obsd. with an estd. IC50 of 0.06 nM. An LNA gapmer was found to be the most efficient **single-stranded** antisense **oligonucleotide**, with an IC50 of 0.4 nM being 175-fold lower than that of commonly used **phosphorothioates** (IC50 .apprx.70 nM). In contrast, the efficiency of a 2'-O-methyl-modified **oligonucleotide** (IC50.apprx.220 nM) was 3-fold lower compared with the **phosphorothioate**. The high potency of siRNAs and chimeric LNA-DNA **oligonucleotides** make them valuable candidates for cell culture and in vivo applications targeting the VR1 mRNA.
IT **15181-41-6, Phosphorothioate**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(RNA; gene silencing using locked nucleic acids, 2'-O-Me RNA, **phosphorothioates** and siRNA)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitrn 7

L75 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:339079 HCAPLUS
DOCUMENT NUMBER: 139:1495
TITLE: Antisense technologies. Improvement through novel chemical modifications
AUTHOR(S): Kurreck, Jens
CORPORATE SOURCE: Institut fur Chemie-Biochemie, Freie Universitat Berlin, Berlin, 14195, Germany
SOURCE: European Journal of Biochemistry (2003), 270(8), 1628-1644
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English
AB A review. Antisense agents are valuable tools to inhibit the expression of a target gene in a sequence-specific manner, and may be used for functional genomics, target validation and therapeutic purposes. Three types of anti-mRNA strategies can be distinguished. Firstly, the use of **single stranded** antisense-**oligonucleotides**; secondly, the triggering of RNA cleavage through catalytically active **oligonucleotides** referred to as ribozymes; and thirdly, RNA interference induced by small interfering RNA mols. Despite the seemingly simple idea to reduce translation by **oligonucleotides** complementary to an mRNA, several problems have to be overcome for successful application. Accessible sites of the target RNA for **oligonucleotide** binding have to be identified, antisense agents have to be protected against nucleolytic attack, and their cellular uptake and correct intracellular localization have to be achieved. Major disadvantages of commonly used **phosphorothioate** DNA **oligonucleotides** are their low affinity towards target RNA mols. and their toxic side-effects. Some of these problems have been solved in "second generation" nucleotides with alkyl modifications at the 2' position of the ribose. In recent years valuable progress has been achieved through the development of novel chem. modified nucleotides with improved properties such as enhanced serum stability, higher target affinity and low toxicity. In addn., RNA-cleaving ribozymes and deoxyribozymes, and the use of 21-mer double-stranded RNA mols. for RNA interference applications in mammalian cells offer highly efficient strategies to suppress the expression of a specific gene.
IT **15181-41-6, Phosphorothioate**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(comparison of different antisense strategy)
REFERENCE COUNT: 131 THERE ARE 131 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitrn 8

L75 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:609425 HCAPLUS
DOCUMENT NUMBER: 139:241236
TITLE: A comparison of gene repair strategies in cell culture using a lacZ reporter system
AUTHOR(S): Nickerson, H. D.; Colledge, W. H.
CORPORATE SOURCE: Department of Physiology, University of Cambridge, Cambridge, UK
SOURCE: Gene Therapy (2003), 10(18), 1584-1591
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Synthetic **oligonucleotides** and DNA fragments of less than 1 kilobase (kb) have been shown to cause site-specific genetic alterations in mammalian cells in culture and in vivo. We have used a lacZ reporter gene system to compare the efficiency of episomal and chromosomal gene repair in human embryonic kidney epithelial cells (HEK293), Chinese Hamster Ovary fibroblasts (CHOK1), human bronchial epithelial cells (16HBE), and mouse embryonic stem (ES) cells. The lacZ gene contains a G to A nucleotide change, (Glu to Lys mutation) that abrogates .beta.-galactosidase activity. We compared the efficiency of different gene repair methods to correct this mutation and restore .beta.-galactosidase activity. We evaluated PCR-generated double-stranded DNA fragments of 0.52-1.9 kb, **single-stranded** DNA **oligonucleotides** of 20, 35, or 80 bases contg. internal **phosphorothioate** links, and a 68 base RNA:DNA **oligonucleotide**. All of the **oligonucleotides** and DNA fragments showed some gene repair ability with an episomal plasmid. Short DNA fragments of 0.52 kb or greater gave the highest frequencies of episomal gene repair while **single-stranded** DNA **oligonucleotides** gave the highest frequency of chromosomal repair. In the context of a chromosomal target, antisense DNA **oligonucleotides** gave 5-fold higher frequencies of gene repair than their sense counterparts. The RNA:DNA chimeric **oligonucleotide** gave little or no gene repair on either a chromosomal or episomal target.
IT **15181-41-6, Phosphorothioate**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(comparison of gene repair strategies in cell culture using a lacZ

reporter system)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitrn 9

L75 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:658292 HCAPLUS
DOCUMENT NUMBER: 137:196646
TITLE: Defined DNA sequences amplifiable with a universal primer pair for use in labeling materials for identification
INVENTOR(S): Brown, Tom; Thelwell, Nichola; Maxwell, Paula; Maxwell, Paul; Whiting, Paul
PATENT ASSIGNEE(S): Crime Solutions Limited, UK
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002066678	A2	20020829	WO 2002-GB759	20020220
WO 2002066678	A3	20030530		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2001-4163 A 20010220
AB A method of uniquely identifying an object by labeling it with a DNA sequence is described. The DNA sequence has a terminal region including a moiety that can be used to attach it to a substrate. Adjacent to this is a sequence by which the DNA can be released from the substrate, such as a restriction enzyme cleavage site. The remainder of the DNA is the unique identifier that includes a pair of primer binding sites sepd. by a defined and unique DNA sequence. The DNA may also contain base analogs or have a modified backbone that will prevent degrdn. of the label by nucleases. The DNA may also be **single-stranded** with the immobilization region in the loop of a stem loop structure. The partially double stranded region may serve as a primer for an initial amplification. Amplification and sequencing of the unique sequence identifier can be used to demonstrate ownership.
IT **15181-41-6D, Thiophosphate**, nucleic acid conjugates
RL: TEM (Technical or engineered material use); USES (Uses)
(for immobilization of **oligonucleotide** label; defined DNA sequences amplifiable with universal primer pair for use in labeling materials for identification)

=> d ibib abs hitrn 10

L75 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:575095 HCAPLUS
DOCUMENT NUMBER: 137:106042
TITLE: Nuclease-based method for detecting and quantitating **oligonucleotides**
INVENTOR(S): Yu, Zhengrong; Baker, Brenda F.; Wu, John
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002059137	A1	20020801	WO 2001-US49702	20011023

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1337547 A1 20030827 EP 2001-994359 20011023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2000-705587 A 20001103
WO 2001-US49702 W 20011023

AB The invention concerns a method for quantitating an **oligonucleotide** in a sample of bodily fluid and/or ext. is provided. The method comprises contacting an **oligonucleotide** with a probe comprising a detectable marker and a binding moiety; placing the fluid or ext. in contact with a solid support to which a binding partner of the binding moiety is attached; contacting the fluid or ext. with a **single-strand** specific nuclease to degrade probe which is not hybridized to the **oligonucleotide**; and detecting a label assocd. with the marker. The method provides or the detection and/or localization of **oligonucleotides**, including administered modified **oligonucleotides**, for therapeutic and/or pharmacokinetic purposes.

IT **15181-41-6**, **Phosphorothioate**
RL: PRP (Properties)
(nuclease-based method for detecting and quantitating **oligonucleotides**)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitrn 11

L75 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:522052 HCAPLUS
DOCUMENT NUMBER: 137:89420
TITLE: Single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA)
INVENTOR(S): Bandaru, Rajanikanth; Kumar, Gyanendra
PATENT ASSIGNEE(S): Molecular Staging, Inc., USA
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053780	A2	20020711	WO 2002-US5	20020104
WO 2002053780	A3	20030522		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003044794	A1	20030306	US 2001-910372	20010720
US 6635425	B2	20031021		
EP 1347988	A2	20031001	EP 2002-705674	20020104

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2003207323	A1	20031106	US 2003-465759	20030619

PRIORITY APPLN. INFO.:
US 2001-259918P P 20010105
US 2001-910372 A 20010720
WO 2002-US5 W 20020104

AB The present invention provides a novel method for ligation of oligonucleotides contg. 5'-phosphorothioates on complementary templates by the action of DNA ligases. This reaction is readily applied to the synthesis of a single stranded circular DNA contg. a phosphorothioate directed ligation reaction by ATP dependent DNA ligase reaction is similar to conventional 5'-phosphate ligation. The utility of enzymic ligation in

probing specific sequences of DNA is also described. The present invention also provides a novel non-enzymic ligation of 5'-phosphorothioates that has been applied to the synthesis of single strand phosphorothioate and phosphate circular DNA. A process for detecting the presence of a mismatch in an otherwise complementary pair of oligonucleotides is disclosed using an enzyme-based technique which shows the presence of a mismatch by failing to form a ligated single stranded DNA circle that can optionally be amplified using std. methods of rolling circle amplification.

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L75 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
IC ICM C12Q001-68
CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 13
ST genotyping SNP single nucleotide polymorphism DNA high throughput assay; human genomic DNA SNP genotyping rolling circle amplification method; oligonucleotide rolling circle amplification nucleic acid
IT Thermus thermophilus
(DNA ligase from; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Escherichia coli
Rhodothermus marinus
Thermus scotoductus
(DNA ligase; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Bacillus phage .phi.29
Coliphage T4
Coliphage T7
(DNA polymerase; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Primers (nucleic acid)
RL: ARG (Analytical reagent use); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(DNA, Amplifluor, fluorescent labeled; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Genome
(DNA; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Alleles
(biallelic SNPs; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT RNA
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(bridging oligonucleotides contg.; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Peptides, biological studies
Primers (nucleic acid)
Proteins
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(closed circle oligonucleotides conjugates to; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Human
(genomic DNA polymorphisms; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Conformation
(hairpin loop, in oligonucleotide; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Enzymes, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(mRNA-capping, single-stranded circular oligonucleotides synthesis using; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT Glass, uses

Plastics, uses
RL: DEV (Device component use); USES (Uses)
(oligonucleotide attached to solid support contg.; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT Deoxyribonucleotides
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(open circle oligonucleotides and bridging oligonucleotides contg.; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT DNA
RL: ARG (Analytical reagent use); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(primer, Amplifluor, fluorescent labeled; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT Nucleic acid amplification (method)
(rolling circle amplification; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT Genetic polymorphism
(single nucleotide; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT Genotyping (method)
Nucleic acid hybridization
(single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT DNA
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT Probes (nucleic acid)
RL: ARG (Analytical reagent use); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT Oligonucleotides
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(single-stranded circular, bridging, synthesis of; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT Phosphorothioate oligonucleotides
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(single-stranded circular, synthesis of; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT 9015-85-4, DNA ligase
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(E. coli, Thermus, Rhodothermus marinus, T4, single-stranded circular oligonucleotides synthesis using; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT 9012-90-2D, DNA polymerase, Klenow fragment
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(E. coli, phage T4 or T7, .phi.29, rolling circle amplification using; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT 56-65-5, ATP, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(as DNA ligase cofactor; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

IT 7786-30-3, Magnesium chloride (MgCl2), biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(in ligation reaction buffer; single-stranded circular oligonucleotide

probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT 25952-53-8, EDC
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(in single-stranded circular oligonucleotide synthesis; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT 9037-46-1, Exonuclease I
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(ligation reaction products treated with; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT 7704-34-9, Sulphur, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(of 5'phosphorothioate group not used as bridging atom for single-stranded circular oligonucleotide synthesis; circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT 9012-90-2, Taq DNA ligase 37259-52-2, Ampligase 37353-39-2
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(single-stranded circular oligonucleotides synthesis using; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))
IT 440688-20-0 440688-21-1 440688-22-2 440688-23-3 440688-24-4, 5: PN: WO02053780 SEQID: 5 unclaimed DNA 440688-25-5, 6: PN: WO02053780 SEQID: 6 unclaimed DNA 440688-26-6, 7: PN: WO02053780 SEQID: 7 unclaimed DNA 440688-27-7, 8: PN: WO02053780 SEQID: 8 unclaimed DNA 440688-28-8 440688-29-9 440688-30-2 440688-31-3 440688-32-4 440688-33-5 440688-34-6 440688-35-7 440688-36-8 440688-37-9 440688-38-0 440688-39-1 440688-40-4
RL: PRP (Properties)
(unclaimed nucleotide sequence; single-stranded circular oligonucleotide probes for detection of polymorphisms in nucleic acids by rolling-circle amplification (RCA))

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L75 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:90226 HCAPLUS
DOCUMENT NUMBER: 136:145278
TITLE: Use of modified oligonucleotide to down-regulate gene expression
INVENTOR(S): Agrawal, Sudhir; Diasio, Robert B.; Zhang, Zhang
PATENT ASSIGNEE(S): Hybridon, Inc., USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008420	A2	20020131	WO 2001-US18338	20010606
WO 2002008420	A3	20021017		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6608035	B1	20030819	US 2000-587934	20000606

PRIORITY APPLN. INFO.:
US 2000-587934 A 20000606
US 1994-328520 A2 19941025
US 1996-709910 B2 19960909
US 1996-758005 B1 19961127

AB Disclosed is a method of down-regulating the expression of a gene in an animal, wherein a pharmacol. formulation comprising a chimeric oligonucleotide complementary to the gene is orally administered to an animal. The oligonucleotide administered has at least one

phosphorothioate internucleotide linkage and at least one alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester internucleotide linkage.

IT 15181-41-6, Phosphorothioate
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(internucleoside linkage; use of modified oligonucleotide to down-regulate gene expression)

=> d ind 12

L75 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
IC ICM C12N015-11
ICS C07H021-00; A61K031-7125; A61P025-28; A61P031-00; A61P033-00
CC 1-12 (Pharmacology)
Section cross-reference(s): 3, 14
ST modified oligonucleotide drug gene expression regulation
IT Lymphoma
(Burkitt's; use of modified oligonucleotide to down-regulate gene expression)
IT Trypanosoma cruzi
(Chagas' disease from; use of modified oligonucleotide to down-regulate gene expression)
IT Leukemia
(T-cell, adult; use of modified oligonucleotide to down-regulate gene expression)
IT Oligonucleotides
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(acetamidate linked; use of modified oligonucleotide to down-regulate gene expression)
IT Ameba
(amebiasis; use of modified oligonucleotide to down-regulate gene expression)
IT Gene
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cellular, oligonucleotide is complementary to; use of modified oligonucleotide to down-regulate gene expression)
IT Disease, animal
(cryptoporidiosis, trichomoniasis; use of modified oligonucleotide to down-regulate gene expression)
IT Gene
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression; use of modified oligonucleotide to down-regulate gene expression)
IT Filaria
(filariasis; use of modified oligonucleotide to down-regulate gene expression)
IT Disease, animal
(foot-and-mouth disease; use of modified oligonucleotide to down-regulate gene expression)
IT Pathogen
Virus
(gene, oligonucleotide is complementary to; use of modified oligonucleotide to down-regulate gene expression)
IT Intestine, disease
(giardiasis; use of modified oligonucleotide to down-regulate gene expression)
IT Human herpesvirus 3
(herpes zoster from; use of modified oligonucleotide to down-regulate gene expression)
IT Ascarid
(infestation with, Ascariasis; use of modified oligonucleotide to down-regulate gene expression)
IT Pharynx, neoplasm
(nasopharynx, carcinoma; use of modified oligonucleotide to down-regulate gene expression)
IT Human herpesvirus
(oral and genital; use of modified oligonucleotide to down-regulate gene expression)
IT Drug delivery systems
(oral; use of modified oligonucleotide to down-regulate gene expression)
IT Wart

(papilloma; use of modified oligonucleotide to down-regulate gene expression)
IT Oligonucleotides
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(phosphoramidite linked; use of modified oligonucleotide to down-regulate gene expression)
IT Schistosoma
(schistosomiasis from; use of modified oligonucleotide to down-regulate gene expression)
IT Toxoplasma gondii
(toxoplasmosis from; use of modified oligonucleotide to down-regulate gene expression)
IT AIDS (disease)
Alzheimer's disease
Blood plasma
Drug metabolism
Hepatitis
Influenza
Malaria
Mammalia
Parasite
Pneumocystis
Trichinella
Trichomonacides
(use of modified oligonucleotide to down-regulate gene expression)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(use of modified oligonucleotide to down-regulate gene expression)
IT Oligonucleotides
Phosphorothioate oligonucleotides
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(use of modified oligonucleotide to down-regulate gene expression)
IT Human herpesvirus 3
(varicella from; use of modified oligonucleotide to down-regulate gene expression)
IT Papilloma
(warts; use of modified oligonucleotide to down-regulate gene expression)
IT Fever and Hyperthermia
(yellow; use of modified oligonucleotide to down-regulate gene expression)
IT 463-77-4, Carbamic acid, biological studies 993-13-5 3812-32-6, Carbonate, biological studies 7664-38-2D, Phosphoric acid, triesters, biological studies 13598-36-2D, Phosphonic acid, alkyl 15181-41-6, Phosphorothioate 16481-04-2, Carboxy methyl ester 22638-09-1, Phosphoramidate
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(internucleoside linkage; use of modified oligonucleotide to down-regulate gene expression)
IT 393599-15-0 393599-16-1 393599-17-2 393599-18-3 393599-19-4
393599-20-7 393599-21-8 393599-22-9 393599-23-0 393599-24-1
393599-25-2 393599-26-3 393599-27-4 393599-28-5 393599-29-6
RL: PRP (Properties)
(unclaimed nucleotide sequence; use of modified oligonucleotide to down-regulate gene expression)

=> d ibib abs hitrn 13

L75 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:457395 HCAPLUS
DOCUMENT NUMBER: 137:259481
TITLE: Separation of Synthetic Oligonucleotide Dithioates from Monothiophosphate Impurities by Anion-Exchange Chromatography on a Mono-Q Column
AUTHOR(S): Yang, Xianbin; Hodge, Richard P.; Luxon, Bruce A.; Shope, Robert; Gorenstein, David G.
CORPORATE SOURCE: Sealy Center for Structural Biology and Department of Human Biological Chemistry & Genetics, University of Texas Medical Branch at Galveston, TX, 77555-1157, USA
SOURCE: Analytical Biochemistry (2002), 306(1), 92-99
CODEN: ANBCA2; ISSN: 0003-2697
PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal
LANGUAGE: English
AB A method using a strong anion-exchange liq.-chromatog. column, Mono-Q, has been developed for high-resoln. anal. and purifn. of oligonucleotide dithioates, which were synthesized by an automated, solid-phase, phosphorothioamidite chem. High-resoln. sepn. of oligonucleotide phosphorodithioates from monothiophosphate impurities was obtained. High-resoln. sepn. was also demonstrated at pH 8. The sepn. of oligonucleotide dithioates was found to be linearly dependent on the no. of sulfurs for the same sequence length. Thiocyanate, SCN-, as eluting anion, can be used to purify oligonucleotides contg. a high percentage of phosphorodithioate linkages in lower salt concns. and provides better sepn. than chloride as eluting anion.
IT 15181-41-6P, Phosphorothioate
RL: BYP (Byproduct); PREP (Preparation)
(mono-, di-; sepn. of synthetic oligonucleotide dithioates from monothiophosphate impurities by anion-exchange chromatog. on a mono-Q column)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind 13

L75 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
CC 9-3 (Biochemical Methods)
Section cross-reference(s): 6
ST monoQ column oligonucleotide dithioate chromatog purifn; monothiophosphate oligonucleotide phosphorodithioate sepn
IT pH
(8, sepn. at; sepn. of synthetic oligonucleotide dithioates from monothiophosphate impurities by anion-exchange chromatog. on a mono-Q column)
IT Ion exchange chromatography
(high-performance; sepn. of synthetic oligonucleotide dithioates from monothiophosphate impurities by anion-exchange chromatog. on a mono-Q column)
IT **Phosphorothioate oligonucleotides**
RL: PUR (Purification or recovery); **PREP (Preparation)**
(sepn. of synthetic oligonucleotide dithioates from monothiophosphate impurities by anion-exchange chromatog. on a mono-Q column)
IT 302-04-5, Thiocyanate, uses
RL: NUU (Other use, unclassified); USES (Uses)
(eluting anion of; sepn. of synthetic oligonucleotide dithioates from monothiophosphate impurities by anion-exchange Chromatog. on a mono-Q Column)
IT 15181-41-6P, Phosphorothioate
RL: BYP (Byproduct); PREP (Preparation)
(mono-, di-; sepn. of synthetic oligonucleotide dithioates from monothiophosphate impurities by anion-exchange chromatog. on a mono-Q column)
IT 131159-51-8, Mono Q HR 10/10
RL: NUU (Other use, unclassified); USES (Uses)
(sepn. of synthetic oligonucleotide dithioates from monothiophosphate impurities by anion-exchange chromatog. on a mono-Q column)

=> d ibib abs hitrn 14

L75 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:868734 HCAPLUS
DOCUMENT NUMBER: 136:1591
TITLE: Genotyping methods to detect DNA sequence polymorphisms and haplotypes
INVENTOR(S): Stanton, Vincent P., Jr.
PATENT ASSIGNEE(S): Variagenics, Inc., USA
SOURCE: PCT Int. Appl., 166 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001090419	A2	20011129	WO 2001-US16577	20010523
WO 2001090419	A3	20030710		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6475736 B1 20021105 US 2000-696998 20001025
PRIORITY APPLN. INFO.: US 2000-206613P P 20000523
US 2000-696998 A2 20001025
US 2000-697013 A2 20001025
US 2000-697028 A2 20001025

AB Methods for detg. genotypes and haplotypes of genes are claimed. Also described are single nucleotide polymorphisms (SNPs) and haplotypes in the ApoE gene and their use in methods of this invention. Methods of the invention involve allele enrichment methods such as allele capture, allele-specific amplification, and allele-specific restriction endonuclease digestion. Allele capture means phys. sepn. of either single-stranded or double-stranded DNA. This can be accomplished by protein or nucleic acid reagents, such as disabled restriction enzymes, zinc-finger DNA-binding proteins, and covalent crosslinking agents, which have affinity for specific alleles. The captured complexes are then sepd. from the nucleic acid mixt. by reagents such as antibody-coated beads or streptavidin. Allele-specific amplification can be accomplished by strand obstruction, such as formation of stable secondary structures, or modified primers such as covalently crosslinkable primers. Lastly, allele-specific restriction methods for genotyping can be accomplished by triplex-mediated protection, primer-mediated creation of polymorphic restriction sites, and other variations, followed by amplification, direct nucleotide sequencing, or capture and size or sequence anal. Allele-specific primers were designed to det. haplotypes of nucleotide 186 T/C and 597 A/G polymorphisms in the dihydropyrimidine dehydrogenase gene. The primers are allele-specific because they induce hairpin loop formation when the "correct" nucleotide is present at the polymorphic site. The hairpin loop structure inhibits annealing of new primers and further amplification. PCR products were digested with BsrDI restriction endonuclease and analyzed by agarose gel electrophoresis. A T/C SNP at genomic site 21250 in the human ApoE gene results in a cysteine to arginine substitution at position 176 of the ApoE protein. For genotyping the T/C SNP, a loop primer and reverse primer were designed to amplify the target and introduce FokI and FspI restriction enzyme cleavage sites. Digestion with FokI and FspI produced allele-specific DNA fragments which were sequenced by mass spectrometry. Fourteen polymorphic sites for the ApoE gene and exptl. derived haplotypes for some or all of these polymorphisms are provided.

=> d ind 14

L75 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
IC ICM C12Q001-68
CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 13
ST genotyping polymorphism haplotype allele DNA binding complex restriction endonuclease; human gene ApoE SNP genotype haplotype PCR sequence analysis
IT Gene, animal
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(APOE; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Quaternary structure
(DNA triplex, allele-specific; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Ligands
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(DNA-binding; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Primers (nucleic acid)
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(DNA; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Enzymes, biological studies
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(RecA; genotyping methods to detect DNA sequence polymorphisms and

haplotypes)
IT Molecular association
(allele-specific DNA-binding; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Hydrogen bond
(allele-specific; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT RNA
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(aptamer; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Peptide nucleic acids
Proteins
Transcription factors
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(biotinylated or immobilized; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT DNA
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(double-stranded; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Alleles
Crosslinking
Genotypes
Genotyping (method)
Immunoassay
Nucleic acid amplification (method)
PCR (polymerase chain reaction)
RFLP (restriction fragment length polymorphism)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Gene, animal
cDNA
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Oligonucleotides
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Peptide nucleic acids
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT **Phosphorothioate oligonucleotides**
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Primers (nucleic acid)
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Proteins
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Transcription factors
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Peptides, biological studies
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(histidine-contg., ligand tag; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Oligonucleotides
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(immobilized; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Oligonucleotides
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(labeled, biotinylated; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Magnetic particles
(ligand tag; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Antibodies
Avidins
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(ligand tag; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Conformation
(loop, nucleic acid, D-loop, allele-specific; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT DNA sequence analysis
(mass spectrometric; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Nucleic acid bases
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(mass-modified; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Imaging
(optical mapping; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Nucleic acid bases
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pairing, allele-specific; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT DNA
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(primer; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(restriction endonuclease cleavage site; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Polyamides, biological studies
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(sequence-specific DNA-binding; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Genetic polymorphism
(single nucleotide; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT DNA
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(single-stranded; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Separation
(size selection; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Immunoassay
(solid-phase; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Proteins
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(zinc finger-contg., biotinylated or immobilized; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT Proteins
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(zinc finger-contg.; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT 9012-90-2, DNA polymerase
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(T4 and I, exonuclease; genotyping methods to detect DNA sequence polymorphisms and haplotypes)

IT 66-97-7, Psoralen 22542-10-5D, complexes, biological studies 146237-51-6 146237-52-7 146237-53-8
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(crosslinking agent; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT 9026-89-5, Dihydropyrimidine dehydrogenase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT 9037-44-9, Escherichia coli exonuclease III 9075-08-5, Restriction endonuclease 37228-74-3, Exonuclease 37367-70-7, Lambda exonuclease 58513-62-5, Nuclease, bacteriophage T7 exodeoxyribo- 81295-34-3, Restriction endonuclease PvuII 81458-03-9, Restriction endonuclease FokI 85340-94-9, Bal31 exonuclease 92228-44-9, Restriction endonuclease NcoI 103780-20-7, NotI restriction endonuclease 107824-63-5 135340-89-5, Restriction endonuclease N.BstNBI 174632-11-2, Restriction endonuclease BsgI 189088-83-3, Restriction endonuclease BsrDI
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT 58-85-5, Biotin 7440-02-0, Nickel, biological studies 9013-20-1, Streptavidin
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(ligand tag; genotyping methods to detect DNA sequence polymorphisms and haplotypes)
IT 9025-82-5, Phosphodiesterase
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(snake venom type I; genotyping methods to detect DNA sequence polymorphisms and haplotypes)

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L75 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:115526 HCAPLUS
DOCUMENT NUMBER: 130:292382
TITLE: High sequence fidelity in a non-enzymic DNA autoligation reaction
AUTHOR(S): Xu, Yanzheng; Kool, Eric T.
CORPORATE SOURCE: Department of Chemistry, University of Rochester, Rochester, NY, 14627, USA
SOURCE: Nucleic Acids Research (1999), 27(3), 875-881
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The success of **oligonucleotide** ligation assays in probing specific sequences of DNA arises in large part from high enzymic selectivity against base mismatches at the ligation junction. We describe here a study of the effect of mismatches on a new non-enzymic, reagent-free method for ligation of **oligonucleotides**. In this approach, two **oligonucleotides** bound at adjacent sites on a complementary strand undergo autoligation by displacement of a 5'-end iodide with a 3'-**phosphorothioate** group. The data show that this ligation proceeds somewhat more slowly than ligation by T4 ligase, but with substantial discrimination against single base mismatches both at either side of the junction and a few nucleotides away within one of the **oligonucleotide** binding sites. Selectivities of >100-fold against a single mismatch are obsd. in the latter case. Expts. at varied concns. and temps. are carried out both with the autoligation of two adjacent linear **oligonucleotides** and with intramol. autoligation to yield circular "padlock" DNAs. Application of optimized conditions to discrimination of an H-ras codon 12 point mutation is demonstrated with a **single-stranded** short DNA target.
IT 15181-41-6, **Phosphorothioate**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(autoligation by displacement of a 5'-end iodide with a 3'-**phosphorothioate** group; high sequence fidelity in a non-enzymic DNA autoligation reaction)
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind 15

L75 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 6, 9
ST nonenzymic DNA autoligation reaction high sequence fidelity
IT Codons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(12, application of optimized conditions to discrimination of an H-ras codon 12 point mutation is demonstrated; high sequence fidelity in a non-enzymic DNA autoligation reaction)
IT DNA
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(autoligation; high sequence fidelity in a non-enzymic DNA autoligation reaction)
IT Mutation
(base-mismatching, ligation proceeds more slowly than ligation by T4 ligase, but with discrimination against single base mismatches; high sequence fidelity in a non-enzymic DNA autoligation reaction)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-Ha-ras, application of optimized conditions to discrimination of an H-ras codon 12 point mutation is demonstrated; high sequence fidelity in a non-enzymic DNA autoligation reaction)
IT DNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(circular, autoligation of two adjacent linear **oligonucleotides** and with intramol. autoligation to yield circular "padlock" DNAs; high sequence fidelity in a non-enzymic DNA autoligation reaction)
IT Mutation
(point, application of optimized conditions to discrimination of an H-ras codon 12 point mutation is demonstrated; high sequence fidelity in a non-enzymic DNA autoligation reaction)
IT **15181-41-6, Phosphorothioate**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(autoligation by displacement of a 5'-end iodide with a 3'-**phosphorothioate** group; high sequence fidelity in a non-enzymic DNA autoligation reaction)
IT 20461-54-5, Iodide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(autoligation by displacement of a 5'-end iodide with a 3'-**phosphorothioate** group; high sequence fidelity in a non-enzymic DNA autoligation reaction)

=> d ibib abs hitrn 16

L75 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:623647 HCAPLUS
DOCUMENT NUMBER: 121:223647
TITLE: Enzymic preparation of single-stranded DNA containing nuclease-resistant modified nucleotides using **phosphorothioate**-containing primers
INVENTOR(S): Nikiforov, Theo; Knapp, Michael R.
PATENT ASSIGNEE(S): Molecular Tool, Inc., USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9416090	A1	19940721	WO 1994-US771	19940118
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN.				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5518900	A	19960521	US 1993-155746	19931123
AU 9461262	A1	19940815	AU 1994-61262	19940118

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     AU 674211         B2   19961212
     EP 679190         A1   19951102       EP 1994-907855   19940118
     EP 679190         B1   20030502
        R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
     JP 08505535       T2   19960618       JP 1994-516386   19940118
     JP 3330946        B2   20021007
     AT 239090         E    20030515       AT 1994-907855   19940118
PRIORITY APPLN. INFO.:                  US 1993-5061     A  19930115
                                        US 1993-155746   A  19931123
                                        WO 1994-US771    W  19940118
AB   A method for generating single-stranded nucleic acid mols. that contain
     nuclease-resistant modified nucleotides and so are resistant to
     5'.fwdarw.3'-exonucleases are described. The method involves synthesizing
     the nucleic acid by primer extension using phosphorothioate
     -contg. primers. A pair of primers with one of them having a
     phosphorothiate-rich 5'-region and the other not contg.
     phosphorothioate nucleotides are used to amplify the target
     sequence. The amplification products are then digested with a
     5'.fwdarw.3'-nuclease with the hydrolysis of all of the nucleic acids
     present except for the amplification products contg. the
     phosphorothiate-rich primer. These products can be used in DNA sequencing
     and in the detn. of genetic polymorphism, esp. single base polymorphisms.
     If the phosphorothiates are placed at the 3'-end of the primer, then any
     residual primers in the reaction can be hydrolyzed with a
     5'.fwdarw.3'-nuclease to prevent further amplification.


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L75  ANSWER 16 OF 17  HCAPLUS  COPYRIGHT 2003 ACS on STN
IC   ICM  C12P019-34
CC   3-1 (Biochemical Genetics)
ST   nuclease resistant single stranded DNA
IT   Deoxyribonucleic acid sequence determination
     Polymerase chain reaction
        (enzymic prepn. of single-stranded DNA contg. nuclease-resistant
        modified nucleotides using phosphorothioate-contg. primers)
IT   Genetic polymorphism
        (single base, detn. of; enzymic prepn. of single-stranded DNA contg.
        nuclease-resistant modified nucleotides using phosphorothioate
        -contg. primers)
IT   Deoxyribonucleic acids
     RL: BUU (Biological use, unclassified); RCT (Reactant); BIOL (Biological
     study); RACT (Reactant or reagent); USES (Uses)
        (single-stranded; enzymic prepn. of single
        -stranded DNA contg. nuclease-resistant modified nucleotides
        using phosphorothioate-contg. primers)
IT   Nucleotides, biological studies
     RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL
     (Biological study); PREP (Preparation); USES (Uses)
        (oligo-, deoxyribo-, thiophosphate-
        linked, primers; enzymic prepn. of single-stranded DNA contg.
        nuclease-resistant modified nucleotides using phosphorothioate
        -contg. primers)
IT   Deoxyribonucleic acids
     RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP
     (Preparation)
        (thiophosphate-linked, single-stranded,
        nuclease resistant; enzymic prepn. of single-stranded
        DNA contg. nuclease-resistant modified nucleotides using
        phosphorothioate-contg. primers)
IT   79121-99-6, 5'.fwdarw.3'-Exonuclease
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); BIOL (Biological study)
        (phage T6 or .lambda.; enzymic prepn. of single-stranded DNA
        contg. nuclease-resistant modified nucleotides using
        phosphorothioate-contg. primers)


=> d ibib abs hitrn 17

L75  ANSWER 17 OF 17  HCAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:        1992:229075  HCAPLUS
DOCUMENT NUMBER:         116:229075
TITLE:                   Phosphorothioate-based site-directed
                         mutagenesis for single-stranded
                         vectors
AUTHOR(S):               Sayers, Jon R.; Eckstein, Fritz
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CORPORATE SOURCE: Abt. Chem., Max Planck Inst. Exp. Med., Heidelberg, D-6900/1, Germany
SOURCE: Directed Mutagen. (1991), 49-69. Editor(s): McPherson, M. J. IRL: Oxford, UK.
CODEN: 57RUAL
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 22 refs. The **phosphorothioate**-based **oligonucleotide**-directed mutagenesis method is based on the observation that certain restriction endonucleases are incapable of hydrolyzing **phosphorothioate** internucleotidic linkages. Thus, double-stranded DNA contg. **phosphorothioate** linkages in one strand only may be nicked in the non-substituted strand. In this mutagenesis procedure the mismatch **oligonucleotide** primer is annealed to the (+)strand of a **single-stranded** circular phage DNA. The primer is extended by a polymn. reaction in which one of the natural deoxynucleoside triphosphates is replaced by the corresponding deoxynucleotide 5'-O-(1-**thiotriphosphate**), dNTP.alpha.S. Thus, **phosphorothioate** groups are incorporated exclusively into the (-)strand of the newly synthesized RF-IV DNA. This results in a strand asymmetry which may be exploited. The methods, scope, and limitations of the procedure are discussed.
IT **15181-41-6, Phosphorothioate**
RL: BIOL (Biological study)
(for site-directed mutagenesis of **single-stranded** DNA vectors)

=> d ind 17

L75 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
CC 3-0 (Biochemical Genetics)
Section cross-reference(s): 9
ST mutagenesis site directed **phosphorothioate** review
IT Genetic vectors
(**single-stranded** DNA, site-directed **phosphorothioate**-based mutagenesis of)
IT Mutation
(site-specific, **phosphorothioate**-based, for **single-stranded** DNA vectors)
IT **15181-41-6, Phosphorothioate**
RL: BIOL (Biological study)
(for site-directed mutagenesis of **single-stranded** DNA vectors)